

Clinical Presentation of Severe COVID-19 Disease in Children and Adolescents

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COVID-19 and Kids
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Introduction

- Novel coronavirus noted in cluster of pneumonia cases in Wuhan (Hubei Province, China) in December 2019
- New virus identified and named SARS-CoV-2, and disease designated as COVID-19
- Rapid spread in China and worldwide
- WHO declared pandemic on March 11, 2020
- As of January 16th 2021:
 - Cumulative cases: 93.9 million+
 - Cumulative deaths: 2million+
- Children/adolescents account for only small proportion of COVID cases
 - 2.1-12% per National Statistics (Asia, Europe, North America)

American Academy of Pediatrics. Children and COVID-19: State-Level Data Report. Available at: <https://services.aap.org/en/pages/2020-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/> (Accessed on January 05, 2021).

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Disease Burden – Severity of Illness of COVID-19 in Children

- Incidence and mortality**
 - Less likely to develop severe illness
 - At risk for severe illness and complications
- Hospitalization rates in US (weekly):**
 - Low compared to adults: 23 vs 413/100,000 (12/26/20)
 - But rates in children are increasing
 - ~5% require hospitalization
 - Among hospitalized 30% required ICU care, 6-9% mechanical ventilation

CDC COVID-NET: <https://www.cdc.gov/coronavirus/2019-nCoV/covid-data/covid-net/purpose-methods.html>
Kim L, et al. *MMWR*. 2020;69(2):2081-2086.
Bailey LC, et al. *JAMA Pediatrics*. 2020. PMID: 33226415. Epub 2020/1/24. eng.

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COVID-19 and Healthcare Disparities

- On average 4x higher infection rate for adults and children of racial and/or ethnic minority groups compared to non-hispanic whites
- Disparities in disease severity have also been well documented: on average 3 out of every 4 children hospitalized with COVID-19 and/or MIS-C come from racial or ethnic minority groups
- These inequalities are driven by a combination of societal- and individual-level factors → Access to care and equitable distribution of therapeutic interventions

Goyal MK, et al. *Pediatrics*. 2020;146(4). PubMed PMID: 32759379. Epub 2020/08/08. eng.
Dufort EM, et al. *N Engl J Med*. 2020;383(4):347-58.
Fernandes DM, et al. *J Pediatr*. 2020.

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How to Recognize COVID-19 in Children?

- Incubation period:** average (range) of days (2-14 days)
- Signs or symptoms:**
 - non-specific
 - Difficult to differentiate from other infections or non-infectious causes
- Asymptomatic: 16% - 50% → symptom-based screening for identification of SARS-CoV-2 in children not useful

Characteristic	Total, nonhospitalized and hospitalized (n = 177)	Nonhospitalized (n = 125)	Hospitalized (n = 44)	P	Hospitalized, noncritical care (n = 36)	Hospitalized, critical care (n = 8)	P
Symptoms present at the time of visit							
Fever	118 (66)	82 (65)	34 (77)	.06	27 (77)	7 (88)	.57
Sore throat or congestion	17 (44)	16 (50)	1 (25)	.004	1 (28)	1 (12)	.26
Cough	99 (56)	83 (66)	16 (36)	.003	15 (44)	4 (50)	.57
Shortness of breath	27 (15)	18 (14)	1 (2)	.04	2 (6)	1 (12)	.53
Dizziness or vomiting	27 (15)	26 (21)	1 (2)	.39	1 (3)	2 (25)	.36
Mutiple	25 (14)	21 (16)	4 (9)	.27	2 (6)	2 (25)	.39
Chest pain	16 (9)	13 (10)	3 (7)	.22	4 (11)	2 (25)	.40
Loss of sense of taste and/or smell	15 (8)	13 (10)	2 (5)	.28	2 (6)	0 (0)	1.00
Headache	25 (14)	24 (18)	1 (2)	.01	1 (3)	0 (0)	1.00

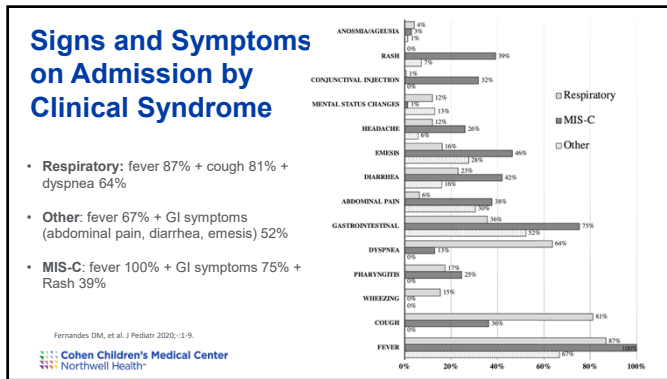
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Clinical Spectrum of COVID-19 in Hospitalized Children

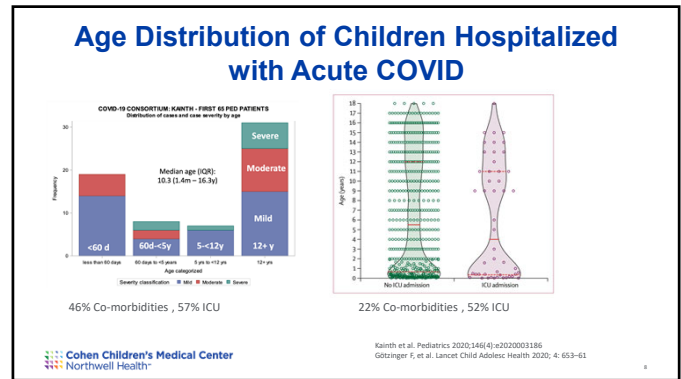
- Acute COVID disease**
 - Respiratory disease
 - Other non-respiratory presentations
- Multisystem inflammatory syndrome in children (MIS-C)**
 - Rare complication of COVID in children
 - Associated with shock and multiorgan failure requiring ICU care
 - UK: paediatric inflammatory multisystem syndrome temporally associated with SARS CoV2 (PIMS-TS)
 - Case definitions vary depending on country and region, an internationally accepted case definition is still evolving

Fernandes DM, et al. *J Pediatr* 2020;1-9

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Acute Respiratory Illness

	With presence of LRTI	Abnormal Radiographs if obtained	Need for Respiratory support among those with LRTI	ARDS among those with LRTI	Death
Zachariah n=50	50%	70%	64%, IMV 36%	?	N=1
Kainth n=65	52%	54%	65%, IMV 13% ECMO n=1	6%	N=1
Fernandes n=281	51%	49%	58%, IMV 18% ECMO n=1	17%	N=7
Göttinger n=363	39%	47%	52%, IMV 18% ECMO n=1	3%	N=2

- Radiographic findings: variable → ground glass opacities (CT); B/L or unilateral patchy infiltrates; focal infiltrates; pleural effusions, pneumothorax
- Duration of IMV: median 5-9 days (IQR 2-27days)
- Patients with ARI compared to MIS-C cases:
 - Older: median age 14y vs 7y
 - More co-morbidities incl obesity

Zachariah P, et al. JAMA Pediatrics October 2020, Volume 174, Number 10
Kainth M, et al. Pediatrics 2020;146(4):e2020003186
Göttinger F, et al. Lancet Child Adolesc Health 2020; 4: 653-61
Fernandes DM, et al. J Pediatr 2020; 1-9
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Laboratory Findings of COVID-19

- Variable
- Lymphopenia (neutropenia) 44% - 72%
- ALC did not differ significantly in patients with and without severe disease

Potential markers of severe disease — elevated WBC and inflammatory markers (eg, CRP, procalcitonin, interleukin 6, ferritin, D-dimer) at admission or during hospitalization

Table 2. Laboratory Values for Patients With and Without Severe Disease

Laboratory studies (normal values)	Peak values, mean (range)		P value
	Nonsevere (n = 41)	Severe (n = 9)	
C-reactive protein (≤10 mg/dL)	4.45 (0.027-25.7)	18.825 (12.69-25.78)	<.001
Procalcitonin (≤0.08 ng/mL)	0.74 (0.04-7.44)	5.3 (0.13-29.89)	.03
Ferritin (≤150 ng/mL)		432.55 (178-1374)	
Interleukin 6 (≤5 pg/mL)		139.52 (11.2-315.0)	
D-dimer (≤0.5 µg/mL)	NA*	4.87 (0.95-18.775)	NA
Partial thromboplastin time (23.9-34.7 s)		47.77 (32.4-108.5)	
Prothrombin time (11.9-14.4 s)		17.32 (13.7-20.7)	

Zachariah P, et al. JAMA Pediatrics 2020
Kainth M, et al. Pediatrics 2020;146
Fisher G, et al. Ann Intensive Care 2020
Fernandes DM, et al. J Pediatr 2020

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Profiles of Children Requiring Intensive Care

	CCMC N=30	US/CA multicenter study N=48
Median age	9.5 (3-13)	13 (4.2-16.6)
Comorbidities	77%	83%
On presentation		
Respiratory	50%	73%
Circulatory	20%	4%
Organ system failure		
Single	64%	63%
≥2	47%	23%
Resp. support	64%	81%
IMV	27%	38%
ECMO	3%	2%
Vasoactive drugs	10%	25%
CRRT	7%	0
Death	3%	4%

Fisher G, et al. Ann Intensive Care 2020
Shekerdemian LS, et al. N Engl J Med 2020
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What Are Risk Factors for Severe Disease?

Most information based on observational studies

- US/CA ICU study: 83% had co-morbidities
- Analysis of deceased: 75% had co-morbidities pediatric patients

MV analysis of risk factors for severe respiratory disease (≠ICU care >48H); N=143

- Age (per 1-year decrease) 1.09 (1.02-1.16)
- Obesity (ref=no obesity) 3.39 (1.26-9.10)
- WBC (per unit increase) 1.11 (1.03-1.20)
- O2 sat <90% 4.01 (1.14-14.15)
- B/L infiltrates 3.69 (1.46-9.32)

Shekerdemian LS, et al. JAMA Pediatr 2020;174(9):660-673
Eliker D, et al. JAMA 19 September 2020 / Vol. 323, No. 10
Fernandes DM, et al. J Pediatr 2020; 9

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Expert panel guidance on monoclonal antibody therapy from 29 North American institutions

Limited observational evidence for increased risk for hosp./severe dx in children/adolescents:

- obesity
- profound immunocompromise or hypogammaglobulinemia
- chronic cardiac disease
- neurodevelopmental disorders or 'medical complexity'
- sickle cell disease

Insufficient evidence

- Mild-moderately immunocompromised
- diabetes mellitus

No evidence

- Asthma
- Chronic kidney disease

Wolf L, et al. J Ped Infect Dis Soc; pna1375

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Management of COVID-19 in Children

General Care	Therapeutics
<p>Hospital admission:</p> <ul style="list-style-type: none"> Severe or critical LRTI At risk for severe disease Infants < 30 days old with fever <p>Supportive care:</p> <ul style="list-style-type: none"> Resp. Support Fluid and electrolytes Monitoring for cytokine release syndrome (RR, SO₂, biomarkers → CRP, Pct, d-dimer, ferritin, LDH, IL-6) Consider thromboprophylaxis 	<ul style="list-style-type: none"> Remdesivir <ul style="list-style-type: none"> approved in US for children ≥12y and ≥40kg EUA: for children <12y but >3.5kg ongoing single arm open-label trial (safety, efficacy, PKs) Corticosteroids (hypoxia, need for resp. support) Baricitinib + remdesivir: EUA for children ≥2y Bamlanivimab; Casirivimab and Imdevimab: EUA ≥12y Immune modulators e.g. anakinra, tocilizumab

Goldenberg NA, et al. J Thromb Haemost. 2020;18:3099–3105.
Chotso K, et al. J Pediatr Infect Dis Soc. pii:1515

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WHAT IS MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN?

Multisystem inflammatory syndrome in children (MIS-C) is a new health condition associated with COVID-19.

SEEK CARE IF YOUR CHILD HAS PERSISTENT FEVER PLUS ANY OF THESE SYMPTOMS:

- lethargy or decreased activity
- Abdominal pain, diarrhea, or vomiting
- Conjunctivitis, or red or pink eyes
- Rash, cracked lips or hoarse voice
- Swollen hands or feet
- Loss of appetite
- Rash

IF YOUR CHILD IS SEVERELY ILL, GO TO AN EMERGENCY ROOM OR CALL 911 IMMEDIATELY.

For more information, call 811 or visit cyc.gov/coronavirus.

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Multisystem Inflammatory Syndrome in Children

- Rare complication (prolonged fever, inflammation, multiorgan failure incl shock)**
 - Acute COVID 322 per 100,000 vs MIS-C 2 per 100,000.
 - Most reported from Europe, Canada, US, South Africa but not from China or other Asian countries
 - Median age 8-11 years; mostly (>70%) previously healthy
 - Black (25-45%) and hispanic (30-40%) disproportionately affected compared to Asian (3-28%) and white (15-25%)
- Pathophysiology:**
 - Post-infectious complication secondary to Immunodysregulation
 - Delayed occurrence, diagnostic profile: 60% ab+, PCR+; 34% ab+, PCR+; 5% ab-, PCR-
 - Clinical similarities to Kawasaki disease (KD), macrophage activation syndrome (MAS), and cytokine release syndrome.
 - Differentiate acute COVID vs MIS-C vs Kawasaki Dx by cytokine profile
 - The mechanisms by which SARS-CoV-2 triggers the abnormal immune response are unknown

Dufort EM, et al. N Engl J Med 2020;383:347
Feinstein LR, et al. N Engl J Med 2020;383:334
Consiglio et al. 2020, Cell 183, 968–981
Gruher et al. 2020, Cell 183, 982–995
Shorio et al. J Clin Invest. 2020;130(11):5967-5975.

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Case Definitions for Multisystem Inflammatory Syndrome in Children

MIS-C associated with COVID-19	PIMS-TS	MIS-C associated with COVID-19
Organization or publication: WHO ¹	Royal College of Pediatric and Child Health ²	US Centers for Disease Control and Prevention ³
Age: 0-19 years	Child (age not specified)	>21 years
Inflammation: Fever and elevated inflammatory markers for 3 days or more	Fever and elevated inflammatory markers	Fever and elevated inflammatory markers
Main features: Two of the following: (A) rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet); (B) hypotension or shock; (C) features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin or N-terminal pro-B-type natriuretic peptide); (D) evidence of coagulopathy (elevated prothrombin time, partial thromboplastin time, and elevated D-dimer); and (E) acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)	Single or multiple organ dysfunction (shock or respiratory, renal, gastrointestinal, or neurological disorder; additional features (appendix 6 pp 3-4))	Clinically severe illness requiring hospitalization; and multi-system (two or more) organ involvement (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, or neurological)
Exclusion: Other microbial cause of inflammation	Any other microbial cause	Other plausible alternative diagnoses
SARS-CoV-2 status: Positive RT-PCR, antigen test, or serologic or any central with patients with COVID-19	RT-PCR positive or negative	Positive RT-PCR, serologic or antigen test; or COVID-19 response within the past 4 weeks before symptom onset

Jiang L, et al. Lancet Infect Dis 2020; 20: e276-88

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How Do Children with MIS-C Present?

- 100% Persistent fevers (median duration four to six days)
- 60 - 100% GI symptoms (abdominal pain, vomiting, diarrhea)
 - appendicitis?, terminal ileitis, colitis
- 45 - 76% Rash
- 30 - 81% Conjunctivitis
- 27 - 76% Mucous membrane involvement
- 29 - 58% Neurocognitive symptoms (headache, lethargy, confusion)
- 21 - 65% Respiratory symptoms
- 10 - 16% Sore throat
- 8 - 17% Myalgia
- 9 - 16% Swollen hands/feet
- 6 - 16% Lymphadenopathy

Capone C, et al. J Pediatr. 2020 Sep;224:141-145.
Kauchik A, et al. Pediatr Infect Dis J. 2020;39:e340
Radaa T, et al. Pediatr Respi Rev. 2020
Feinstein LR, et al. N Engl J Med 2020;383:334

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Laboratory findings

<p>Elevated inflammatory markers:</p> <ul style="list-style-type: none"> 90 - 100% C-reactive protein (CRP) 75 - 80% ESR 67 - 100% D-dimer 80 - 100% Fibrinogen 55 - 76% Ferritin 80 - 95% Procalcitonin 80 - 100% Interleukin-6 (IL-6) 	<p>Abnormal blood cell counts:</p> <ul style="list-style-type: none"> 80 - 95% Lymphocytopenia 68 - 90% Neutrophilia 70% Mild anemia 31 - 80% Thrombocytopenia <p>Other abnormal markers:</p> <ul style="list-style-type: none"> 48 - 95% Hypoalbuminemia 62 - 70% Mildly elevated liver enzymes 10 - 60% Elevated LDH 70% Hypertriglyceridemia
<p>Elevated cardiac markers:</p> <ul style="list-style-type: none"> 50 - 90% Troponin 73 - 90% BNP or NT-pro-BNP 	

Health Day, Year

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Organmanifestations and Complications in MIS-C

- 32 – 76% Shock
- 22 – 64% Criteria met for complete Kawasaki dx
- 51 – 90% Myocardial dysfunction
- 12% Arrhythmia
- 28 – 52% Acute respiratory failure
- 8 – 52% Acute kidney injury
- 24 – 57% Serositis (small pleural, pericardial, and ascitic effusions)
- 5 – 21% Hepatitis or hepatomegaly
- 6 – 7% Encephalopathy, seizures, coma, or meningoencephalitis

Echocardiography

- Depressed LV function (30-40%)
- Coronary artery (CA) abnormalities including dilation or aneurysm (8-19%)
- Mitral valve regurgitation
- Pericardial effusion

C Overlap in Organ-System Involvement

Capone C, et al. J Pediatr. 2020 Sep;234:141-145.
 Kaushik A, et al. Pediatr Infect Dis J. 2020;39:e340.
 Radio T, et al. Pediatr Resour Rev. 2020.
 Feldstein LR, et al. N Engl J Med 2020;383:334

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Spectrum of MIS-C Disease

An emerging new spectrum of SARS-Cov2 in children- not just COVID

Dividing MIS-C into 3 clinical categories by "latent class analysis" (n=570)

- Pure MIS-C**
Median age 9y. Many organ systems, esp. CV (100%) & GI (98%). More: abd pain, shock, myocarditis, lymphopenia, markedly elevated CRP, ferritin, troponin, proBNP. Positive SARS-CoV-2 serology (98%)
- Acute COVID-19 +/- MIS-C (mixed?)**
Median age 10y. Respiratory (76%), more cough, SOB, pneumonia, ARDS. PCR+ in 84%, mortality 5.3% (highest of 3 groups)
- Kawasaki-like:**
Younger age-median 6y; more: mucocutaneous findings, less: underlying medical conditions, organ system involvement, shock, myocarditis, inflammation markers & cardiac injury. SARS-CoV-2 serology & PCR 34%; SARS-CoV-2 serology only 63%

Michael Levine, Imperial College

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Godfred-Cato S, et al. MMWR 2020;69:1074

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Differentiating MISC from Kawasaki Disease

	MIS-C	Kawasaki Disease
1. Age:	older children and adolescents	infants and young children
2. Race/ethnicity	black, Hispanic	higher incidence in East Asia, children of Asian descent
3. GI Symptoms	++++	++
4. Myocardial dysfunction and shock	++++	+ in patients with KD shock syndrome (5%)
5. Higher CRP, ferritin	++++	+++
6. Lower lymphocyte, platelet counts	++++	++
7. Risk of CA involvement in MIS-C is comparable with the risk in classic KD ???		

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Management

Treatment

- Based on presentation: distributive shock vs cardiac dysfunction vs KD like features
- Shock/ cardiac dysfunction: according to standard protocols (epinephrine, norepinephrine and milrinone)
- CCMC experience: n=33
 - IVIIG: 100%
 - Aspirin: 88%
 - Methylprednisolone: 70%
 - Enoxaparin: 42%
- In case of incomplete response:
 - IVIIG 2nd dose: 30%
 - Anakinra: 12%
 - Tocilizumab: 9%
 - Infliximab: 3%

Outcome

CCMC experience:

- 0 deaths
- Cardiac function at discharge
 - Always normal: 42%
 - Depressed then normalized: 18%
 - Mildly depressed: 27%

Systematic review: n=655 patients

- 11 deaths
- 20% mildly depressed cardiac function

Prognosis unclear at this time
 → Long term follow up studies lacking for now

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Capone C, et al. J Pediatr. 2020 Sep;234:141-145.
 Kaushik A, et al. Pediatr Infect Dis J. 2020;39:e340

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Summary

- Risk for COVID-related morbidity and mortality and need for hospital care is significantly less in children compared to adults
- One third of children requiring hospital care (comparable rate to adults) require intensive care because they may develop respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, and multi-organ system failure
- Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but significant complication, that is still incompletely understood in terms of its pathogenesis and prognosis
- Children with co-morbidities and obesity maybe at an increased risk for severe disease manifestations, more studies needed to describe diagnosis-specific risk profile, and possible clinical interventions and strategies to reduce hospitalization risk
- Longstanding disparities in healthcare highlighted also for children, with a disproportionate negative effect on communities of color

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Thank you for your attention!

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